Supplemental information for

Quantitative Structure Activity Relationship for Inhibition of Human Organic Cation/Carnitine Transporter (OCTN2)

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Supplemental Table S1. Summary table for the Bayesian model. This model was built using 22 training compounds and validated using a leave-one-out cross-validation. Each sample was left out one at a time; a model was built using the remaining 21 compounds, and that model was used to predict the left-out compound. From all 22 predictions, a ROC plot was generated. The area under the curve **(XV ROC AUC)** was calculated.

Best Split was calculated by identifying the split that minimized the sum of the percent misclassified for inhibitors and non-inhibitors, using the cross-validated score for each sample. Using that split, a contingency table is constructed (below), containing the number of true positives (**TP),** false negatives (**FN**), false positives (**FP**), and true negatives (**TN**).

XV ROC AUC	**Best Split**	**TP/FN FP/TN**	**Number of OCTN2 inhibitors**
0.929	-3.512	13/1 1/7	14

Supplemental Table S2. Bayesian model enrichment results. This model was built using 22 training compounds and validated using a leave-one-out cross-validation. From all 22 predictions, an enrichment plot was generated. The percentage of true inhibitors captured at a particular percentage cutoff is tabulated below. For example, in the column labeled "1%", 7.1% of the OCTN2 inhibitors were found in the top 1% of the Bayesian model list, when sorted by Bayesian score. This table illustrates enrichment results. Almost 80% of OCTN2 inhibitors were listed in the top half of Bayesian score values. Percentages that are less than 100% are in **bold**. 14 (63.6%) of the 22 compounds were classed as inhibitors.

	Category %	**1%**	**5%**	**10%**	**25%**	**50%**	**75%**	**90%**	**95%**	**99%**
Percent of the 22 compounds that were inhibitors	63.6%	**7.1%**	**14.3%**	**21.4%**	**42.9%**	**78.6%**	**92.9%**	100%	100%	100%

Supplemental Table S3. Percentile results for Bayesian model. This table shows, for each candidate Bayesian model, the cutoff needed to capture a particular percentage of the good samples. For each cutoff, the estimated percentages of false positives and true negatives for non-good samples is shown. This table is designed to identify the cutoff value that best balances the capture of good samples, while limiting false positives. The rates shown in this table are estimates derived from the cross-validated data. The cutoff which lead to 10% or greater false positives are displayed in **bold** for ease of identification.

99%	**95%**	**90%**	**70%**	**50%**	**30%**	**10%**	**5%**	**1%**
-9.331	-6.203	-4.505	-2.628	-2.628	4.969	6.845	8.543	11.671
59%/41%	**38%**/62%	**27%**/73%	**18%**/82%	6%/94%	2%/98%	1%/99%	1%/99%	1%/99%

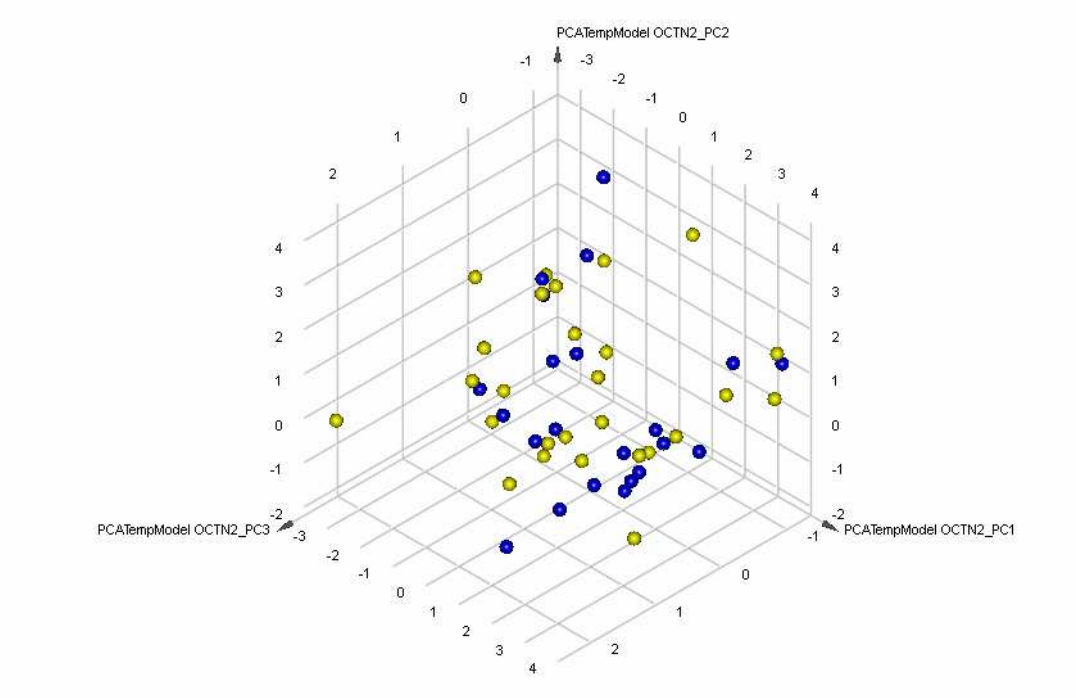
Supplemental Table S4. Predicted Bayesian scores for OCTN2 inhibitors and non-inhibitors.

Number of OCTN2 inhibitors	Mean (±StdDev) predicted Bayesian score of OCTN2 inhibitors	Number of OCTN2 non-inhibitors	Mean (±StdDev) predicted Bayesian score of OCTN2 non-inhibitors
14	1.17 (±4.47)	8	-8.14 (±5.88)

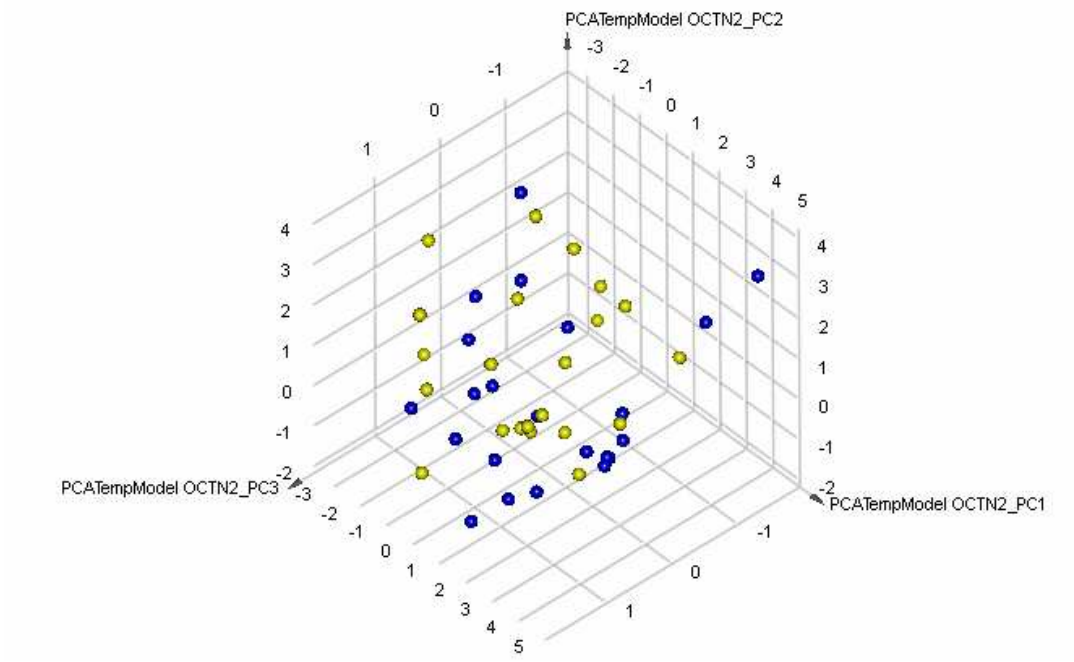
Supplemental Table S5. Pharmacophore coordinates and inter feature distances (Å) described in supplemental Figure S5.

Pharmacophore feature	Hydrogen bond acceptor (HBA)	Hydrophobic	Hydrophobic	Positive Ionizable
Weights	1.59896	1.59896	1.59896	1.59896
Tolerances	1.60 2.20	1.60	1.60	1.60
Coords : X	7.74 10.59	-3.00	1.12	5.75
: Y	4.76 5.06	3.58	2.74	1.05
: Z	1.53 2.43	-0.44	4.88	-0.56
	o--------->	o	o	o
HBA	o---> 3.0 Å			
Hydrophobic	o 11.0 14.0			
Hydrophobic	o 7.7 10.1	6.8		
Positive Ionizable	o 4.7 7.0	9.1	7.3	

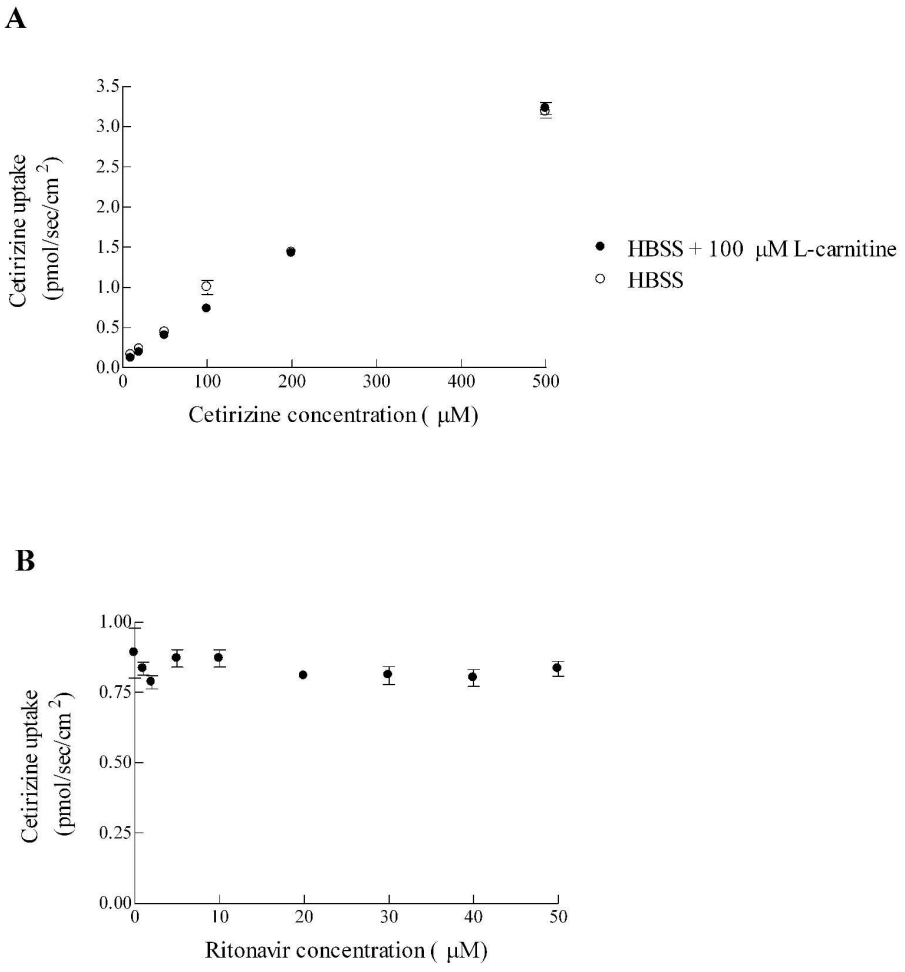
Supplemental Figure S1. PCA of test set using data generated in our laboratory. 82.8% of the variance was explained by three principal components. Yellow spheres = test set; blue = training set.



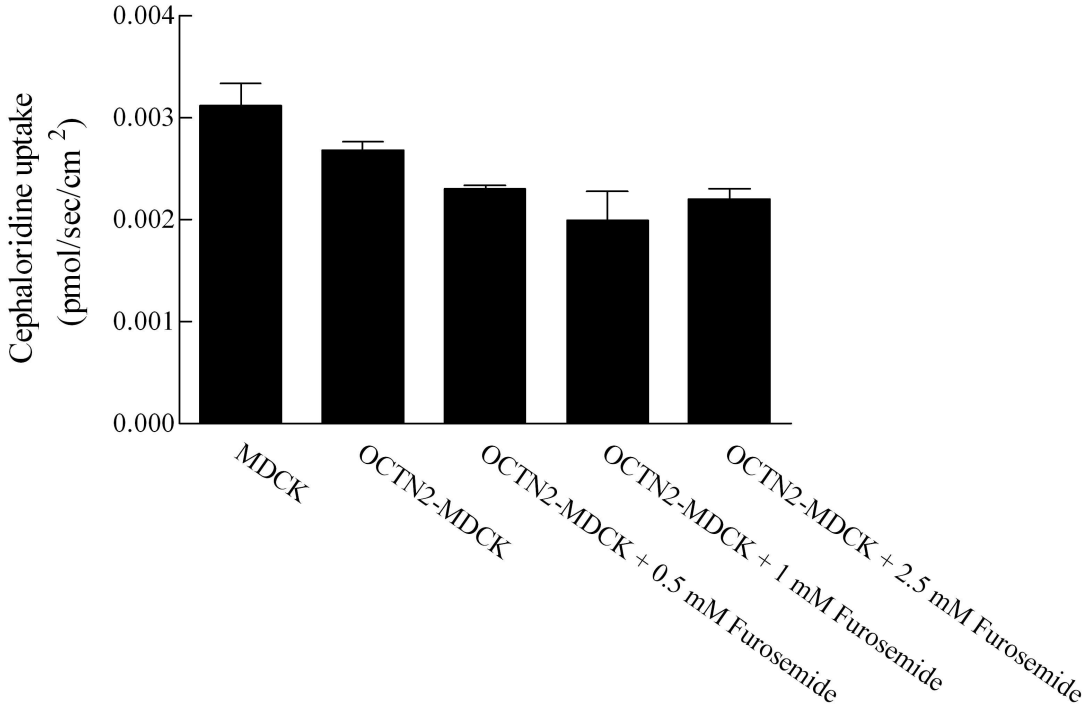
Supplemental Figure S2. PCA of literature test set. 83.6% of the variance explained by three principal components. Yellow spheres = test set; blue = training set.



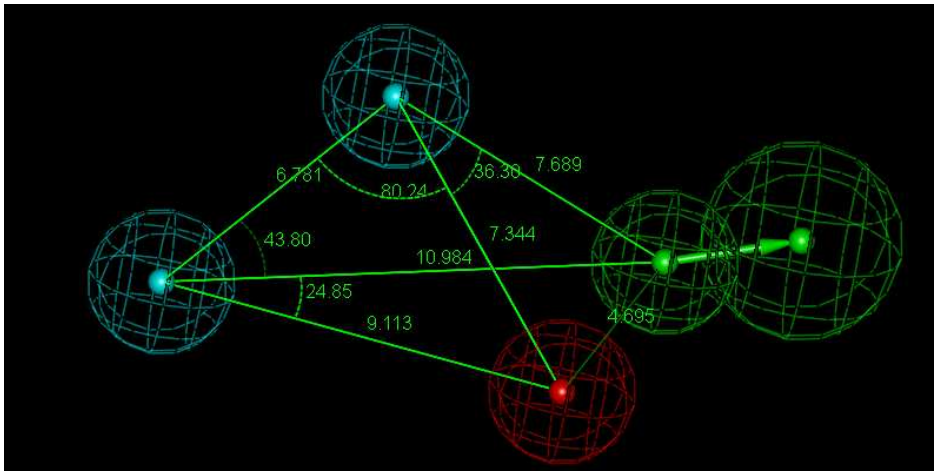
Supplemental Figure S3. A. Cetirizine uptake into OCTN2-MDCK cells in HBSS from 10 – 500 μM in the presence and absence of 100 μM L-carnitine. B. Cetirizine (100 μM) uptake into OCTN2-MDCK cells in HBSS in the absence and presence of ritonavir (1-50 μM).



Supplemental Figure S4. Cephaloridine (0.5 mM) uptake into OCTN2-MDCK cells and MDCK cells in HBSS were determined. Furthermore, cephaloridine (0.5 mM) uptake into OCTN2-MDCK cells in HBSS in the presence of furosemide (0.5 - 2 mM) are plotted.



Supplemental Figure S5. OCTN2 pharmacophore inter-feature distances (Angstroms) and angles (Degrees).



Supplemental Table S6: List of references in manuscript Table 5.

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